

REVIEW ARTICLE

Histological appraisal of lupus nephritis

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ABSTRACT

The importance of renal biopsy in systemic lupus erythematosus (SLE) patients with nephritis resides not only in the diagnosis, but mostly in its role in guiding and assessing therapy. The potential benefits of treatment in lupus nephritis include a dramatic clinical improvement and a direct impact on renal survival. However, these benefits can be achieved only if they are carefully weighed against the complex, prolonged, and potentially toxic treatment regimens. This review on lupus nephritis emphasizes on the histological appraisal of lupus nephritis, which may demonstrate some variations among institutions, but should be clearly defined if one expects to have more useful information for the routine management of patients, as well as in clinical trials.

Key words: Activity index, Chronicity index, Lupus nephritis, Renal biopsy, Systemic lupus erythematosus, WHO classification,

中文摘要

腎活檢對於系統性紅斑狼瘡腎炎患者的重要性，不單在於確診，尤為重要的是對治療提供指導和評估作用。通過治療，患者的臨床徵狀有可能獲得顯著改善，對腎存活率亦有直接影響。為要達到理想的治療效果，必需對治療方案的複雜性、長久性和潛在副作用仔細地作出衡量。本文集中闡述狼瘡性腎炎的組織病理變化和評估。不同的醫療和科研單位對腎活檢的組織學評估或有差異；然而，惟有明確界定每一病理變化，才能有助於病人的診治以至臨床試驗。

INTRODUCTION

Lupus nephritis and IgA nephropathy are by far the two most common conditions encountered in renal biopsies in our institution, and each accounts for over 30% of the cases every year (1,2). The high incidence of IgA nephropathy in biopsies reflects its being the most prevalent glomerulonephritis worldwide, and such nephropathy rarely requires a repeat biopsy (1,3). In contrast, the prevalence of lupus nephritis in biopsies reflects the relatively frequent repeat examination to guide treatment and to assess therapeutic response. Although lupus nephritis is a serious complication of systemic lupus erythematosus (SLE), current therapies may result in dramatic clinical response and in improved renal outcome. However, such benefits can be gained only when they are carefully weighed against the often

prolonged and potentially toxic therapy. While controversies exist over whether biopsy is required for initial treatment, the importance of histological classification and indices in the patient's management is no longer controversial (4).

PATHOGENESIS OF SLE AND LUPUS NEPHRITIS

The pathogenesis of SLE remains obscure. Although genetic and racial predispositions appear to be important, the prevalence and mortality of SLE are strikingly similar in various parts of the world, including China or Hong Kong (2,4,5). The risk factor for lupus nephritis in women is attributed to estrogens, while androgens confer a certain protection. Infective agents and environmental

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factors have always been suspected, but remain unproven (3).

The wide range of autoantibodies produced in SLE with tissue deposition or formation of immune complexes, and the handling defect or "saturation" of the monocyte-phagocytic system, all contribute to renal injury. The effector mechanisms mediated by complements, inflammatory cells, or cytokines leading to renal injury are similar in lupus and in other non-lupus nephritis (4).

CLINICAL MANIFESTATIONS IN LUPUS NEPHRITIS

Renal manifestations in SLE are highly variable, and often not well correlated with renal pathology. Only few patients with SLE show urinary abnormalities early in their course. Proteinuria and nephrotic syndrome are dominant features, but microscopic hematuria is also common. Hypertension is as common in SLE patients with nephritis as in those without. Over half of SLE patients demonstrate some impairment of renal function, but only few present with acute renal failure (4). Tubular dysfunction leads to increased light chains and beta 2-microglobulin excretion, and renal tubular acidosis of both hypokalemic and hyperkalemic types (4). The clinical approach to lupus nephritis must consider the patient as a whole, where extrarenal disease may be dominant. The initial presentations are often non-renal, even in patients who later develop severe nephritis.

ANTIPHOSPHOLIPID ANTIBODIES AND THE "LUPUS ANTICOAGULANT"

The "lupus anticoagulant" activity is a misnomer, since the antiphospholipid antibodies are directed against the beta 2-globulin carrier protein rather than the phospholipid itself. They increase the risk of thrombosis *in vivo* for unknown reason, in contrast to anticoagulation *in vitro*. These antibodies are detected in up to 50% of patients with lupus nephritis, and have been associated with renal and extrarenal thrombosis. However, true lupus anticoagulant exists, due to antibodies to factors VIII, IX, XI and XII, and their presence requires fresh-frozen plasma coverage for renal biopsy.

DIAGNOSIS AND IMMUNOLOGIC TESTS

Although the diagnosis of SLE is usually not difficult, many patients are first suspected for other rheumatic disorders. Routine screening of all proteinuric patients for antinuclear antibodies (ANAs) is helpful. Nephritis is seen in a few patients with mixed connective tissue

disease, but a seropositive anti-Ro and anti-La, and negative anti-dsDNA antibodies confirm the diagnosis. The immunologic tests require at least a positive ANA, but preferably a positive dsDNA. The Farr assay detects high avidity anti-dsDNA antibodies, and both the enzyme-linked immunosorbent assay (ELISA) and the Crithidia Lucile kinetoplast test detect low avidity antibodies. Anti-Sm antibodies are highly specific, but present only in 30% of patients. Low serum complement is common in untreated lupus nephritis, and may reflect active renal lesions. SLE may mimic Henoch-Schönlein purpura with rash on the lower limbs, but assay for anti-neutrophil cytoplasmic antibody (ANCA) can be useful to the diagnosis in the latter condition (4). SLE differs from microscopic polyarteritis by a positive anti-dsDNA serum and a negative anti-myeloperoxidase assay (6).

RENAL PATHOLOGY

The spectrum of lupus nephritis can be very broad, and encompasses all possible glomerular reactions to injury. The WHO classification of lupus nephritis is based on the light microscopy of six predominant glomerular lesions. This classification has been correlated with renal prognosis, and has permitted establishment of successful therapeutic protocols. While essential to the management of lupus, the WHO classification no longer carries prognostic value following treatment (4). A more dynamic assessment of lupus nephritis has been developed at the National Institute of Health (NIH), with the semiquantitative determination of disease activity and

Table 1. Simplified WHO classification of lupus nephritis.

Class I	Minor glomerular abnormality
Class II	Pure mesangial lesions (mesangiopathic)
Class III	Focal segmental lesions (necrosis, sclerosis, or both)
Class IV	Diffuse glomerulonephritis (with/without necrotizing or sclerosing lesions)
Class V	Membranous nephropathy
Class IV	Advanced sclerosing glomerulonephritis

Table 2. Activity and chronicity indices in lupus nephritis (NIH).

Active lesions (maximum score of 24)	
1.	Endocapillary hypercellularity
2.	Necrotizing lesions
3.	Extracapillary proliferation (crescents)
4.	Leukocytes infiltration
5.	Hyaline changes (wire loops, thrombi)
6.	Tubulointerstitial inflammatory cells infiltrate
Chronic lesions (maximum score of 12)	
1.	Glomerular obsolescence
2.	Fibrous crescents
3.	Tubular atrophy
4.	Interstitial fibrosis

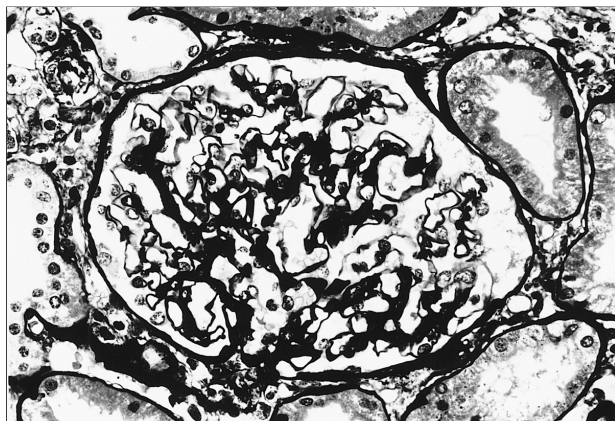


Figure 1. Glomerulus in class II mesangiopathic alteration exhibits intact tufts architecture, and at least mild mesangial matrix expansion and/or three mesangial cells per area. Periodic acid-silver methenamine, x 340.

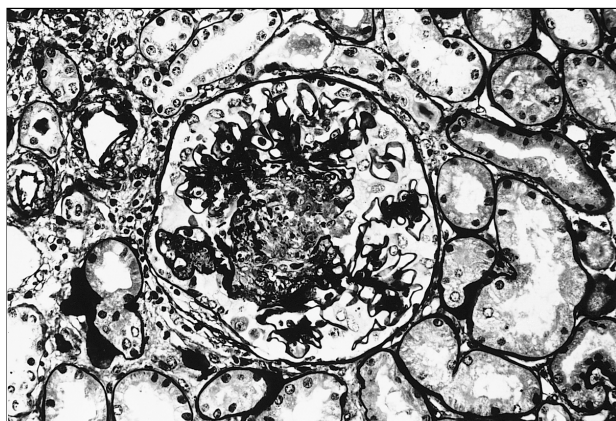


Figure 2. Class III lupus nephritis demonstrates a segmental necrotizing lesion, featuring here capillary wall disruption, nuclear fragmentation, and polymorphs infiltration. Periodic acid-silver methenamine, x 320.

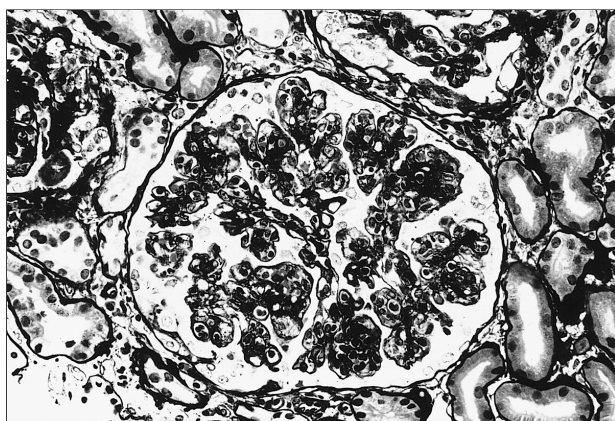


Figure 3. Global endocapillary hypercellularity with extensive obliteration of capillary lumen, and such lesion usually affects most glomeruli in class IV nephritis. Periodic acid-silver methenamine, x 340.

chronicity, which has been correlated with short- and long-term renal outcome, and thus plays an important role in guiding and assessing therapy (4,7). The WHO classification and NIH indices used at the Prince of Wales Hospital are both simplified in table 1 and table 2, respectively.

WHO CLASSIFICATION

This classification deals only with glomerular lesions, with no reflection on tubular or extraglomerular vascular disease. Although the 1995 modified version has improved from the original 1982 WHO classification, it would be unrealistic to believe that any case of lupus nephritis fits exactly into one of the six categories. In fact, many subdivisions in this classification have been made, in an attempt to encompass the frequent morphologic overlapping between the defined categories. These subdivisions have caused some confusions, and have been partly clarified in the 1995 modified classification. We believe that such subdivisions should be simplified to those which are clinically relevant, and useful in predicting renal outcome prior to therapy. In the Prince of Wales Hospital, the histological assessment, which include the classification and appraisal of activity and chronicity indices, is based on a minimum of 10 glomeruli, 5 mm cortex, and three arterioles.

Class I and Class II

Patients with class I or II nephritis may present with modest or even no clinical disease. All patients with class I and most with class II will have a benign course, even without treatment. On histology, class I shows normal glomeruli or glomeruli with minor abnormality, with no distinction made on the presence or absence of immune complexes, which are usually modest in amount. Class II mesangiopathic disease (Fig. 1) refers to mesangial expansion due to either hypercellularity (three or more cell per mesangial area), or sclerosis, or both, associated with mesangial immune complexes.

Class III

Class III is characterized by segmental lesions, which may include necrosis, sclerosis, endocapillary proliferation, crescent or any combination of these lesions (Fig. 2). Based on clinicopathologic observations, we have adopted the subdivision of class III nephritis advocated by some into a low-grade and a high-grade, corresponding to segmental lesions present in less than 50% and in 50% or more of the glomeruli, respectively (8,9). However, the clinical relevance of such subdivisions remains to be established by prospective studies, which may require the use of activity indices in the subdivisions (8-10). Such a high-grade class III requires similar treatment as in class IV nephritis.

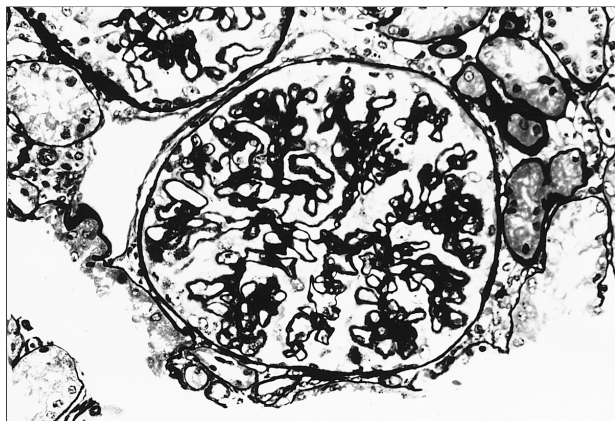


Figure 4. Lupus membranous nephropathy in pure form with mildly thickened capillary wall and inconspicuous spikes. Such lesion is better demonstrated in immunofluorescence or ultrastructural studies. Periodic acid-silver methenamine, x 320.



Figure 5. A capillary loop exhibiting both subepithelial and subendothelial (*) dense immune deposits, and the extent of subendothelial deposition has been correlated with prognosis. Uranyl acetate and lead citrate, x 12600.

Class IV

Class IV represents the most common renal lesions biopsied, reflecting their overt clinical manifestations, and is characterized by diffuse and global endocapillary hypercellularity with or without cellular crescent (Fig. 3). While this global glomerular lesion may mask features of other classes, this would not alter the immediate treatment. Other features commonly seen include "wire-loops", hematoxyphil bodies, necrotizing lesions, which may be superimposed with sclerosis, disruption of Bowman's capsule and glomerular distortion in the more protracted case.

Class V

Lupus membranous nephropathy may be in pure form with classical spikes and dome pattern on silver stain, and characterized by predominant subepithelial immune

complexes, or be mixed with or masked by lesions from other classes (Fig. 4). Renal vein thrombosis may complicate such class V lesions.

The 1995 modification of the WHO classification had reduced the number of subdivisions, and made it simpler to use and reproduce among institutions. Our simplified classification has gone one step further, and eliminated the subdivisions, since secondary histological features that make these subdivisions can be included in the assessment of activity and chronicity indices. For examples, class V nephritis associated with focal segmental necrotizing lesions or with global endocapillary proliferation, formerly classified as Vc or Vd respectively, are now simplified as classes III and V, or classes IV and V, respectively. The principle is to identify, in a case of lesions, from various classes in a first step, and subsequently report the classes that are clinically relevant. For example, a case with lesions of classes II, III, IV and V is reported as class IV and V.

Keeping in mind that a biopsy represents the renal lesions at one point in time, and may not reflect the dynamic process of a nephritis, and that lesions overlap between classes, the concept of progression or "transformation" among WHO classes of lupus nephritis appears to be over-simplified. However, interpreted as such, these "transformations" are common, especially following successful therapy (4,11). In fact, only histological features useful to guide treatment are relevant, and the activity and chronicity indices are much more informative and important in the management of lupus nephritis. Their role will get more important in clinical trials.

Assessment of Activity and Chronic Indices or Scores

The activity index is scored from all viable glomeruli, excluding the obsolescent ones, and the chronicity index is scored on all glomeruli present in sections. Each activity and chronicity factor is graded on a scale of 0,1, 2,3 on a semiquantitative scale. Endocapillary proliferation, leukocyte infiltration and hyaline changes are graded on the severity of lesion in individual glomeruli. Cellular crescents, necrotizing lesions, glomerular sclerosis (segmental or global) and fibrous crescents are graded as 0 for absence, 1 for less than 25%, 2 for 25% to 50%, and 3 for more than 50% of glomeruli affected. Interstitial infiltrates, tubular atrophy and interstitial fibrosis are graded as 0 for absence, 1 for less than 25%, 2 for 25% to 50%, and 3 for more than 50% of cortical areas affected. As defined by the NIH scoring, cellular crescents and necrosis are weighed by a factor of x2.

Immunopathology and Ultrastructures

Polyclonal immunoglobulins and polytypic complement complexes in basement membrane and mesangium constitute the hallmark of a "full house" pattern, which characterizes lupus nephritis. IgG is predominant among immunoglobulins which are associated with early complements C1q, C4 as well as C3. Other immune reactants such as properdin, complement B, C5b-9, IgE, etc are not routinely used. Electron microscopy shows the often-widespread distribution of dense immune complexes in all three glomerular sites: subendothelium, subepithelium and mesangium, with the former being the most prominent (Fig. 5). Prominent subepithelial deposits are seen in class V nephritis. Tubuloreticular structures are commonly seen, but not specific to lupus nephritis. The fingerprint pattern in dense deposits is distinctive, but only seen in a few cases.

OTHER MORPHOLOGICAL FEATURES

Patients with active nephritis may also demonstrate tubular basement membrane (TBM) immune complex and anti-TBM antibodies, associated with interstitial infiltration by T lymphocytes and monocytes. Tubular infiltration or "tubulitis" is common in active disease, but interstitial fibrosis expands in chronic disease. Tubulointerstitial nephritis may be prominent, progress independently of glomerular lesions, and become determinant in the progression of lupus nephritis. Hyaline changes and fibrinoid lesions of arterioles may be seen, but rarely intrarenal arteriolar thrombi. These lesions are all associated with a poor prognosis. A few patients show thrombotic microangiopathy and depressed plasminogen activators (3,4).

Amyloidosis is rare in lupus, because acute-phase proteins like amyloid A and C-reactive protein do not rise in the plasma during clinical flares. Non-lupus glomerulopathies, including dense-deposit disease, pauci-immune necrotizing glomerulitis, hepatitis B virus, *Escherichia coli*, human immunodeficiency virus, and IgA nephropathy, have been reported (3,12-14).

CLINICOPATHOLOGIC CORRELATIONS

SLE patients without clinical nephritis may show significant glomerular disease in their biopsy, and they may continue to show no clinical nephritis for several years. SLE patients with clinical nephritis must have gone through a period of occult disease, but the proportion of patients with such a subclinical course is unknown. While severe glomerular lesions tend to show severe clinical

manifestations, renal histology cannot be predicted with certainty from the clinical features. WHO biopsy classes are powerful determinants of outcome in untreated patients, but not after treatment. Interstitial changes at the time of biopsy correlate with glomerular filtration rate (GFR) and the renal outcome. The anti-dsDNA antibody levels are similar in all histologic classes.

TREATMENT OF LUPUS NEPHRITIS

In patients with no or minor urine abnormality with class I or II nephritis, treatment is unnecessary. Whether corticosteroids at this point might prevent subsequent severe disease has never been tested. The group with focal proliferative nephritis (class III) or severe diffuse proliferative nephritis (class IV) would benefit most from immunosuppression. There is no clear evidence of improved outcome of membranous nephropathy (class V) after treatment, but some of these patients progress slowly to renal failure. The treatment of lupus nephritis has two facets: one is the induction treatment of severe acute life-threatening disease, with multisystem involvement, and the other is the maintenance treatment of chronic more indolent disease, where protection from the side effects of treatment is increasingly important. The evidence for treating all but the mildest types of lupus nephritis with corticosteroids is very strong (4,9, 15). Corticosteroids may be complicated by peptic ulcers, diabetes, Cushing appearance, osteoporosis, and gonadal failure. Cyclophosphamide may also result in gonadal failure. Azathioprine can be complicated by cholestasis, pancreatitis and marrow failure. Life-threatening infection may include disseminated herpes zoster and cryptococcal meningitis.

Results of Treatment in Lupus Nephritis

The clinical course of lupus can no longer be considered separately from the results of treatment, and the overall mortality and renal survival has markedly improved compared to 30 years ago (4). This has led to almost all patients with lupus nephritis receiving treatment, including those with mild nephritis. The 5-year actuarial survival improved from 17% to 82% in patients with class IV nephritis in 35 years, and from 44% to 82% for all lupus nephritis (4). There is a gratifying response to early treatment, followed by quiescent disease under maintenance therapy. Some patients relapse during quiescent state, and the frequency and intensity of flares have partly been correlated with the intensity and duration of immunosuppression. To date, less than 15% of patients with lupus nephritis progress to end-stage renal failure, and the main causes of death in these patients include sepsis, cerebral lupus, and premature cardiovascular disease. The proportion of end-stage renal patients with "burnt-out" lupus has been exaggerated, as

most patients on dialysis still require immunosuppression (16). Results of transplantation are comparable to other groups of patients, and recurrent disease in allograft is rare. Morphologically, all active glomerular lesions are potentially reversible with complete reversal of the activity (11). The WHO classification after treatment is no longer relevant to prognosis (4).

Factors Influencing Renal Outcome

Clinical factors predicting the outcome in lupus nephritis include serum creatinine, hypertension, and perhaps proteinuria. While controversy exists for age at onset, smoking, black race, and hypercholesterolemia, indices of clinical activity, number of clinical criteria at onset, and the frequency of relapses also predict outcome. The strongest laboratory predictor of outcome is anemia, but low platelet count, low serum complements, and levels of circulating anti-dsDNA antibodies also correlated with a poor prognosis (4).

Histologically, there is little difference in outcome among different WHO classes in treated patients. However, cellular crescents, extensive subendothelial immune deposits (Fig. 5), and tubulointerstitial disease point to a poorer prognosis. Vascular lesions within the biopsy and intraglomerular capillary thrombi have been associated with unfavorable outcomes. Calculation of activity and chronicity indices allows identification of high and low risk groups for a poor outcome, and also permits therapeutic decisions of when to use aggressive treatment (4,9,15).

CONCLUSION AND PERSPECTIVES

The importance of histologic classification and indices of activity and chronicity of lupus nephritis on the management and prognosis of SLE patients is well established and cannot be overemphasized. However, the full impact of renal biopsy in the treatment of lupus nephritis remains to be defined. The evidence supporting an early biopsy and treatment of all but the mildest types of lupus nephritis is very strong, especially if adverse renal outcome is to be avoided by preventing accumulative effect of irreversible renal damage. From a prognostic viewpoint, the morphologic data enhances clinical and serological predictors in the short-term and

long-term assessment of the renal outcome. 'Watchful observation of a mildly abnormal urinary sediment may be a recipe for long-term grief. The risk of renal biopsy pales in comparison with the long-term consequences of watchful waiting' (9).

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